Medical Science

Creatine Supplementation: Effects on athletic performance, cognitive processing, and long-term health consequences. A review of the literature

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ABSTRACT

Creatine is a naturally occurring compound that plays an essential role in cellular energy production. It has important applications in sports nutrition and medical research. Mainly accumulated in skeletal muscle, it facilitates ATP replenishment during strenuous exercise. Supplementation enhances phosphocreatine levels, improving anaerobic performance, muscle strength, and lean body mass, particularly in resistance-trained athletes and high-intensity sports. Beyond its physical benefits, creatine carries the potential for cognitive and therapeutic applications. Evidence underlines improvements in memory, processing speed, and executive function improvements, mostly in older adults and populations with metabolic deficits. Preliminary findings suggest neuroprotective benefits against conditions like Alzheimer's and Parkinson's diseases, though further evidence is needed. Creatine is widely regarded as safe when taken as recommended, and there have been no significant adverse effects on the kidney, liver, or general health in short- or long-term studies. Yet, ethical concerns over its application in adolescent athletes and competitive sports will have to be continually considered. This review highlights the many faces of creatine supplementation, from benefits in physical performance and cognitive support to therapeutic potential. Future research should focus on long-term effects, age- and gender-specific responses, and clinical applications. The neuroprotective properties and optimal dosing protocols deserve further investigation, and their implementation may further cement creatine as a mainstay in effectiveness towards improving physical, cognitive and clinical outcomes in diverse populations.

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1. INTRODUCTION

Creatine, a naturally occurring nitrogenous organic compound, has been a staple in sports nutrition and medical research for decades. Creatine is primarily produced in the kidneys, liver, and pancreas from amino acids like glycine, arginine, and methionine, and it is stored predominantly in skeletal muscle as phosphocreatine, an essential substrate in the regeneration of adenosine triphosphate (ATP) during high-intensity activities (Kreider et al., 2017). While endogenous synthesis supplies a baseline level, dietary sources, particularly red meat and fish, and supplementation significantly increase creatine stores in the body (Pashayee-Khamene et al., 2024). The relative attractiveness of creatine supplementation comes from the relatively strong evidence base, demonstrating increases in anaerobic performance, lean body mass, and recovery in athletes performing resistance training and high-intensity training.

Beyond its effect on physical performance, growing research highlights its neuroprotective and cognitive-enhancing effects. Studies suggest improvements in working memory, executive function, and resilience to cognitive decline linked to ageing or neurological conditions. Creatine also demonstrates promise in the clinical literature, reducing muscle atrophy and oxidative stress during ageing, aiding in recovery and rehabilitation, and even decreasing the severity of trauma to the brain following injury. Despite its proven efficacy, some common misconceptions about creatine exist, including unfounded concerns regarding renal and hepatic toxicity and misunderstanding of optimal timing and dosing (Roschel et al., 2021; Kreider et al., 2017).

Although creatine has been well-studied for its influence on endurance and muscular strength, the benefits of creatine for cognitive functioning- especially in the elderly population and those with neurodegenerative diseases- are fast-growing research areas. This review combines findings on how creatine functions in the brain, appraises its effectiveness across differing populations and discusses optimal supplementation protocols for differing performance outcomes. Additionally, the long-term safety of, and ethical considerations concerning, its use in competitive sports are being explored. Recommendations are then made for future research directions, including long-term effects, gender-specific responses, and creatine's potential role as a neuroprotective agent (Roschel et al., 2021; Kreider et al., 2017).

2. METHODOLOGY

This review collates results from peer-reviewed scientific literature published between January 2017 and August 2024, obtained from database searches of PubMed, Google Scholar, and Scopus using the following search terms: "creatine supplementation", "sports performance", "cognitive enhancement", "neuroprotection", and "ergogenic aids". Article selection was based on set criteria that included study designs like randomised controlled trials (RCTs), systematic reviews, meta-analyses, and cohort studies. Populations studied included healthy individuals, athletes, older adults, and individuals with neurodegenerative diseases, thus allowing a broad assessment of creatine applications.

3. RESULTS AND DISCUSSION

Mechanism of Action

Creatine supplementation strongly affects muscle energy metabolism by increasing phosphocreatine levels, the primary energy reservoir for short, high-intensity muscle activity. The body uses phosphocreatine to replenish ATP (adenosine triphosphate), the primary energy currency inside cells. Therefore, this supplementation increases the capacity to perform fast, explosive movements, enhancing weightlifting, sprinting, and high-intensity interval training (HIIT) (Antonio et al., 2021; Forbes et al., 2022). Aside from its contribution to the replenishment of ATP, creatine has been shown to activate several cellular pathways involved in muscle protein synthesis, notably the mTOR (mechanistic target of rapamycin) pathway, which plays a vital role in cellular growth and repair.

Creatine's involvement in mTOR signalling may explain its reported favourable effects on gains in muscle mass and strength with resistance training (Arazi et al., 2021; Chilibeck et al., 2017). In addition, supplementation with creatine appears to reduce the activity of proteins important for muscle breakdown, such as myostatin, which may help explain other mechanisms contributing to the capacity of creatine to increase muscle hypertrophy (Kreider et al., 2017). Another related key mechanism is that of creatine's cellular hydration

management: By attracting water into muscle cells, creatine has been known to increase the total mass of muscle tissue and, therefore, aid in volumization, augmenting muscle performance.

Indeed, this effect of a hydrated state is most evident in fast-twitch muscle fibre types, which more significantly rely upon anaerobic energy provision (Ribeiro et al., 2021). More recent research points to the possible neuroprotective effects of creatine. In the brain, creatine is involved in ATP production and mitochondrial function and may provide some protection against neurodegenerative diseases. This is particularly relevant for conditions that impair cellular energy metabolism, such as Parkinson's disease and Alzheimer's disease (Forbes et al., 2022).

Effect of Creatine on Exercise Performance

Creatine supplementation improves athletes' performance in anaerobic activity and high-intensity sports. Much research has shown that it increases muscular strength, power output, and endurance in activities involving short spurts of maximal effort. Kreider et al., (2017) examined various aspects of exercise performed with creatine supplementation and from different exercise types. They that creatine does indeed markedly improve performance in sprinting, resistance training, and high-intensity interval training (HIIT). Research has revealed that creatine supplementation can increase maximal strength by approximately 5–15% in trained athletes performing short, high-intensity exercise (Kreider et al., 2017).

In resistance-trained individuals, creatine has been shown to translate into increased muscle hypertrophy and an increase in lean body mass. One study revealed a range of 1–2 kg (2.2–4.4 lbs) increase in lean body mass over 4–12 weeks of supplementation combined with resistance training, depending on the population and training protocol (Kreider et al., 2017). Findings from Mills et al., (2020) emphasize the efficacy of creatine ingestion during resistance training sessions. Over six weeks, physically active young adults supplementing with creatine experienced significant increases in leg and chest press strength compared to a placebo group. Muscle endurance, measured by the number of repetitions to fatigue, also improved more in the creatine group, particularly for the leg press.

These gains were attributed to creatine's ability to enhance intramuscular phosphocreatine stores, facilitating faster ATP resynthesis and recovery between sets (Mills et al., 2020). Likewise, phosphocreatine stores can benefit performance in explosive sports such as sprinting, jumping, and weightlifting because they make it possible to regenerate ATP more quickly during short bursts of high exercise intensity. Creatine supplementation also has a small but meaningful impact on endurance. While the primary gains are in anaerobic work, sorely complaining in endurance-type activities that have repeated bouts of high-intensity efforts, such as those found in playing soccer or rugby, can also see a difference, as seen in several recent studies.

The meta-analytical study by Mielgo-Ayuso et al., (2019) showed significant improvements in overall anaerobic performance (SMD: 1.23; 95% CI: 0.55–1.91; $p < 0.001$), whereby the Wingate test yielded the most pronounced improvements (SMD: 2.26; 95% CI: 1.40–3.11; $p < 0.001$). Moreover, according to a recent meta-analysis, the studies included going on average showed some statistically significant improvements in different performance measures, like repeated sprints, neuromuscular strength, anaerobic power, sprints, agility runs, jump countermovement, dribble test, maximum power test and average power output test (Mielgo-Ayuso et al., 2019).

Table 1 provides a succinct overview of the main results from the meta-analysis and review by Pashayee-Khamene et al., (2024), which discusses the effect of creatine supplementation on exercise performance and body composition. The study pooled data from 143 studies with 3,655 participants and study durations between 4 and 365 days. The study showed more significant improvements in body composition when combined with resistance training, as well as greater effects were observed in resistance training compared to aerobic or no-exercise interventions, increased body mass, and free-fat mass. The effects were more significant in males and younger individuals (Pashayee-Khamene et al., 2024).

Table 1 Summary of Creatine Supplementation Effects on Exercise Performance and Body Composition.

Parameter	Details
Resistance Training Impact	Greater improvements in body composition when combined with resistance training compared to supplementation alone.
Exercise Type Influence	Greater effects were observed in resistance training compared to aerobic or no-exercise interventions.
Effect on Body Mass	Increased body mass (Weighted Mean Difference, WMD:

	0.86 kg; 95% CI: 0.76 to 0.96; $p < 0.05$; $I^2 = 0\%$)
Effect on Fat-Free Mass	Increased fat-free mass (WMD: 0.82 kg; 95% CI: 0.57 to 1.06; $p < 0.05$; $I^2 = 0\%$)
Effect on Body Fat %	Reduced body fat percentage (WMD: −0.28%; 95% CI: −0.47 to −0.09; $p < 0.05$; $I^2 = 0\%$)
Population Differences	Effects more significant in males and younger individuals; limited data on females and older populations.

Cognitive Benefits of Creatine Supplementation

Beyond the physical performance-enhancing effects, creatine supplementation has generated interest in its possible benefits on cognitive function. A systematic review by Avgerinos et al., (2018) examined six randomised controlled trials (RCTs) with 281 participants, revealing evidence that creatine may improve short-term memory and intelligence/reasoning, especially in those facing stress or in older adults. However, data on other cognitive areas, such as attention, executive function, and mental fatigue, showed wide variability. Another interesting finding is that vegetarians showed much more significant improvements in memory-related tasks than omnivores, most likely due to initially lower creatine levels; however, there were no obvious cognitive benefits when given to young, healthy adults.

The findings suggest that creatine supplementation may selectively help cognitive enhancement in special groups of people, while its general effect is still unclear (Avgerinos et al., 2018). Notably, creatine supplementation enhances performance in high-energy-demand tasks, including executive function memory, and reduces mental fatigue. Research has demonstrated that creatine enhances brain bioenergetics by increasing phosphocreatine levels, facilitating ATP regeneration during cognitively demanding activities. A study by Xu et al., (2024) found that creatine supplementation resulted in modest but significant improvements in memory (SMD = 0.31; 95% CI: 0.18–0.44) and processing speed (SMD = −0.51; 95% CI: −1.01 to −0.01), particularly among adults aged 18–60.

However, its impact on overall cognitive function and executive tasks was inconsistent (Xu et al., 2024). Prokopidis et al., (2023) noted significant memory enhancements in older adults (SMD = 0.88; 95% CI: 0.22–1.55), suggesting creatine is more effective in populations with more significant energy deficits. Furthermore, Candow et al., (2023) observed that creatine supplementation improves cognitive performance under metabolic stress conditions, like sleep deprivation, by alleviating mental fatigue and aiding recovery. Sandkühler et al., (2023) reported minor, non-significant effects on executive function and reasoning tasks in vegetarians and omnivores, indicating that dietary creatine levels might affect responsiveness.

Moreover, Forbes et al., (2022) highlighted the potential cognitive effects of creatine ingestion, especially in relation to brain energy metabolism and mitochondrial activity. These effects have the potential to help lower oxidative stress, which is an important driver of neurodegenerative diseases. Although some studies suggest that creatine supplementation may improve cognitive performance under specific conditions, such as sleep deprivation or mental fatigue, the evidence base is still limited and inconsistent with respectively taking an effect in preventing neurodegenerative diseases such as Alzheimer or Parkinson. The review notes that further studies are required to determine whether creatine influences long-term cognitive performance and acts as a neuroprotective factor (Forbes et al., 2022).

Creatine and Injury Prevention

Research has largely investigated creatine supplementation with respect to its performance-enhancing effects, but its injury-prevention potential is still under investigation. Current evidence linking creatine to strengthening tendons, ligaments, or connective tissues is sparse; however, it may indirectly benefit musculoskeletal health (Burke et al., 2023). Candow et al., (2023) found that creatine during resistance training boosts muscle mass and strength, improving joint stability and lowering the risk of injuries from muscle weakness or imbalance. Speaking of recovery, Burke et al., (2023) emphasized that creatine supplementation can reduce exercise-induced muscle damage.

This would result in faster recovery after high-intensity or eccentric workouts, probably reducing the risk of overuse injuries because of prolonged muscle soreness and fatigue (Burke et al., 2023). Furthermore, because creatine is involved in enhancing muscle performance during high-intensity exercise, it may also reduce the risk of injury. Wax et al., (2021) observed that creatine promotes muscle force generation and fibre engagement, which contributes to enhanced resistance to mechanical stress during demanding

physical exercise. While these results offer hope, Wu et al., (2022) pointed out that the potential of creatine for injury prevention is still poorly understood and needs more research to clarify its impact on connective tissues and injury risk.

Creatine in Clinical Populations

Creatine supplementation offers more than benefits for athletic performance; it also opens therapeutic possibilities in many clinical populations. For patients with neurological disorders like Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), creatine may improve muscle strength and functional ability. Mitochondrial dysfunction and decreased production of ATP are characteristic of such disorders; hence, their symptoms include muscle weakness and fatigue. By elevating phosphocreatine, creatine helps in the regeneration of ATP and therefore could reduce symptoms and improve quality of life for these patients (Forbes et al., 2022 ; Dolan et al., 2019).

For populations suffering from muscle wasting, including those undergoing chemotherapy or heart failure, creatine supplementation—especially when paired with resistance training—has increased lean muscle mass, strength, and physical performance. These findings suggest that creatine may be useful in combating muscle atrophy, thus helping with rehabilitation, particularly among older adults susceptible to sarcopenia and frailty (Dolan et al., 2019; Wang et al., 2024). Beyond its muscle health benefits, creatine has antioxidant effects, according to (Arazi et al., 2021). It boosts the body's capacity to lower oxidative stress and supports mitochondrial health. These benefits may promote cellular protection and recovery in oxidative damage scenarios, such as during intense exercise or specific chronic illnesses (Arazi et al., 2021).

Gender and Age-Specific Responses to Creatine Supplementation

Research consistently indicates that creatine supplementation effects vary based on age, gender, and baseline creatine levels. Younger individuals, especially those with lower initial muscle creatine stores, typically see more significant improvements in muscle strength and power from creatine supplementation. A systematic review by Burke et al., (2023) noted a slight edge in muscle hypertrophy and strength gains for younger adults compared to older ones. Nonetheless, older adults also benefit from creatine, particularly in preserving muscle mass and strength during resistance training (Burke et al., 2023). Older adults often receive secondary benefits from creatine supplementation, particularly when combined with resistance training, in terms of great improvements in muscle strength, functional ability, and bone density.

These changes are very important for opposing age-related muscle loss (sarcopenia) and maintaining independence. Forbes et al., (2022) found that integrating creatine supplementation with structured exercise regimens significantly boosted these aspects in older populations. Gender differences in response to creatine are evident, particularly regarding muscle mass gains. Women tend to show smaller increases in muscle hypertrophy than men, likely due to varying initial muscle creatine levels and hormonal influences. However, cognitive enhancements from creatine appear consistent across genders. Both men and women have demonstrated improvements in memory and executive function tasks following creatine supplementation, although the extent and specific areas of cognitive enhancement may differ (Forbes et al., 2022; Forbes et al., 2023).

Dose-Response and Optimal Protocols

The classic method of creatine supplementation is to follow an initial loading phase, which consists of a daily dose of 20 grams per day for 5-7 days, followed by a maintenance phase of 3-5 grams/day. This methodology helps in quickly saturating creatine reserves in the muscle tissue and has also been suggested to enhance the performance benefits associated with supplementation, particularly in the initial stages (Antonio et al., 2021). However, it is shown that low-dose regimes, in which 3 to 5 grams are taken daily without a loading phase, are equally effective in saturating the muscles over an extended period. It has been estimated that this could take 3 to 4 weeks. This approach is much more convenient and economically feasible and, therefore, is often preferred by those looking to escape large initial dosages (Kreider et al., 2017).

Recent findings highlight the possible importance of timing in maximizing the benefits associated with creatine supplementation. Creatine monohydrate is the most studied form, with nearly 99% retention post-ingestion. Post-exercise creatine intake may confer more significant benefits than pre-exercise consumption, as exercise-induced blood flow to muscles enhances nutrient delivery and uptake. When combined with carbohydrates or proteins, creatine absorption can be further augmented due to insulin-mediated transport mechanisms (Ribeiro et al., 2021). Despite these findings, further investigation is necessary to ascertain how exercise type,

age, and gender influence optimal dosing strategies. Individualized protocols that consider these factors may optimize the efficacy of creatine supplementation across varied populations (Kreider et al., 2017; Ribeiro et al., 2021). Table 2 provides an overview of the dosing protocols.

Table 2 Summary of Creatine Supplementation- Dose Protocols

Dosing Protocols	Loading phase: 20–30 g/day for 5–7 days. Maintenance phase: 2–5 g/day for up to 9 weeks. Low-dose protocol: 3 g/day saturates intramuscular stores over ~28 days.
Creatine Forms	Creatine monohydrate is the most studied form, with nearly 99% retention post-ingestion.

Long-Term Effects and Safety Concerns

Creatine supplementation is widely acknowledged as safe when administered within the recommended dosages. According to Kreider et al., (2017), both short-term and long-term supplementation (up to 30 grams per day for 5 years) is well-tolerated among healthy individuals as well as various clinical populations, without adverse effects on renal or hepatic function, hydration status, or overall health. Although short-term studies repeatedly show creatine to be safe, there is limited research on long-term effects, especially with timescales beyond five years. The current evidence highlights the clinical benefits of creatine in promoting neuroprotection and slowing the neurodegenerative processes in Alzheimer's and Parkinson's diseases (Forbes et al., 2022). Candow et al., (2023) emphasize the importance of creatine in supporting brain bioenergetics and suggest its possible application in cognitive health interventions.

Further studies are needed to confirm these results in different populations (Candow et al., 2023). There are also concerns about creatine use in certain populations, such as adolescent athletes. Although creatine supplementation has not been shown to be harmful if taken within safe limits, its ethical implications and use in competitive settings should be further clarified to ensure fairness, as well as safety in sports and high-performance contexts (Kreider et al., 2017; Avgerinos et al., 2018). Additionally, the cognitive benefits of creatine supplementation, including enhancements in memory and attention, are observed to be more prominent during periods of metabolic stress or in populations with lower baseline creatine levels, such as vegetarians or older adults (Candow et al., 2023; Avgerinos et al., 2018). Xu et al., (2024) found moderate evidence for its efficacy in terms of memory and processing speed; more studies are needed to better assess the impact on lowering the risk or delaying cognitive decline.

4. CONCLUSION

Creatine is a versatile compound that could be used for more than just athletic performance. Its main mechanisms—ATP regeneration, cellular hydration, and protein synthesis modulation—contribute to strength, muscle mass, and recovery enhancements. Athletes frequently experience improved anaerobic performance, greater maximal strength, and increased lean body mass, especially during high-intensity or resistance training. Beyond physical performance, creatine has promising cognitive and therapeutic applications. Studies show it can improve memory, processing speed, and executive function, especially in older adults and those who have metabolic or cognitive issues. Early studies suggest potential neuroprotective benefits against conditions such as Alzheimer's and Parkinson's, although more research is necessary to substantiate these findings.

When creatine is taken as recommended, safety concerns are largely unwarranted. Studies back its safety for both short — and long-term use, with no significant adverse effects on the kidney, liver or overall health. However, with ethical concerns, particularly in young recreational athletes and competitive settings, further discussions are essential. There is a need for future studies to examine long term outcomes, gender and age-specific differences and dosing strategies. More research on its neuroprotective effects and more generalized applications might justify the use of creatine as a valuable supplement. By customizing supplementation to meet individual needs, creatine has the potential to significantly enhance physical, cognitive, and clinical outcomes across various populations.

Authors' Contribution

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Michalina Doligalska: Conceptualisation, project administration
Sandra Prolejko: Methodology, data curation
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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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